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Title: Short-term effects of caffeine intake on binocular accommodative facility: a quantitative and qualitative analysis

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Clinical relevance: Caffeine intake has been demonstrated to influence several physiological measures, including some related to eye physiology. The ability to focus at different distances is of paramount importance in real-world situations, and thus, the possible impact of caffeine intake on accommodative facility may have important applications.

Background: This placebo-controlled, double-blind, balanced crossover study aimed to assess the acute effects of caffeine ingestion on the frequency and precision of the binocular accommodative facility.

Methods: 20 university students (21.9 ± 3.4 years) ingested a capsule of caffeine (4 mg/kg) or placebo (300 mg of corn-starch) in two different days and counterbalanced order. The binocular accommodative facility was objectively assessed, using the WAM-5500 binocular open-field autorefractometer, after 60 minutes of capsule ingestion (caffeine/placebo). We also assessed the perceived levels of activation in each experimental condition.

Results: The ingestion of a single administration of caffeine (~ 4 mg/kg) causes an increase in the number of cycles performed per minute ($p = 0.023$, Cohen's $d = 0.55$), whereas no effects were observed for the mean magnitude of accommodative change between the far and near targets ($p = 0.794$), and the percentage of incorrect cycles of accommodation and dis-accommodation ($p = 0.271$ and 0.396, respectively). Participants reported a perceived level of activation of 6.8 ± 1.5 and 7.6 ± 1.8 in the placebo and caffeine conditions, respectively ($p = 0.059$).

Conclusion: Our findings indicate that caffeine intake improves quantitative, but not qualitative, measures of accommodative facility. These results corroborate the impact of caffeine on visual function and suggest that this ergogenic effect of caffeine may be used to enhance visual performance in applied situations.

Introduction

Caffeine is considered to be the central nervous system stimulant most widely consumed nowadays, with approximately 80% of the world's population consuming a caffeinated product every day.[1] The average daily caffeine consumption is highly variable among countries, but it is estimated at ~200mg per day and person.[2,3] High levels of caffeine intake are linked to a wide range of positive outcomes provided by this substance, with the effects on psychomotor and cognitive performance being the most renowned. This improvement in task performance under the effects of caffeine has been attributed to a faster reaction time, an increase in the amount of transmitted information, and a more efficient orientation to the environment.[4,5] Additionally, regular caffeine consumption has beneficial effects for human health status such as a reduced risk of several types of cancer, as well as cardiovascular, metabolic, and neurological conditions.[6]

Previous studies have also demonstrated that caffeine modifies some visual abilities. For example, acute caffeine consumption increases the velocity of rapid eye movements [7] and restores the slow saccadic eye movements in states of low arousal.[8] The accommodative-vergence system is also sensitive to caffeine intake, in particular, an exophoric shift in the distance dissociated phoria,[9] a greater amplitude of accommodation,[10] and lower variability of accommodation[11] have been observed. In addition, caffeine intake has been shown to improve performance in a visual vigilance task, [12,13] and a simple selective visual attention task[5] by facilitating the detection of visual stimuli and response preparation.[14]

In real-world contexts, the visual system does not fixate for a long time on a stationary target, rather we have to alternatively focus on different distances by changing the refractive power of the lens. The ability of the eye to alter accommodation rapidly and accurately is known as the accommodative facility.[15] This visual ability is of paramount importance to succeed in applied scenarios (e.g., sports practice, driving, etc.), and has been proposed as a useful predictor of visual discomfort[16] and academic performance.[17] A reduced accommodative facility has been found in visually symptomatic patients[18] and is used as a diagnostic sign for different accommodative and binocular anomalies.[19] The standard procedure to measure accommodative

facility consists of changing the accommodation level with the use of flipper lenses (usually ± 2.00 D) as soon as a target placed at 40 cm has been focused.[20] However, this method presents a high inter-individual variability since it depends on the subject's criteria for judging when the target is clear/blurry, and the subject's reaction time to indicate that the target is clear and flip the lenses.[21,22] Recently, to minimize these methodological drawbacks, a new objective method has been developed and validated, which permits to objectively and reliably assess the frequency and precision of the accommodative facility by using a binocular open-field autorefractometer.[23]

Due to the lack of scientific evidence about the ergogenic effects of caffeine on the dynamics of the accommodative facility, we have designed a placebo-controlled, double-blind, balanced crossover study, using the previously mentioned method, to determine the short-term effects of caffeine intake on the qualitative and quantitative measures of accommodative facility. Previous studies have shown that caffeine affects the accommodative amplitude and response,[10,13], and therefore, it is reasonable to expect that caffeine ingestion may affect the accommodative facility. We hypothesize that both the frequency and accuracy of the binocular accommodative facility would be improved as a consequence of the acute effects of caffeine intake in comparison to the placebo condition.

Methods

Participants

First, we performed an a-priori power analysis, using the GPower 3.1 software,[24] to calculate the required sample size for this study. For this analysis, we assumed an effect size of 0.30, power of 0.80 and alpha of 0.05. This calculation projected a minimum sample size of 18 participants. Based on this calculation, a total of 20 university students, who consumed one or less caffeine-based beverage per day,[13,25,26] were recruited to participate in this study (twelve women; mean age ± standard deviation: 21.9 ± 3.4 years; and mean weight ± standard deviation: 66.0 ± 10.1 kg). Participants were screened according to the following inclusion criteria: (i) be free of any systemic or ocular disease, (ii) no history of strabismus, amblyopia or refractive surgery, (iii) have

normal or corrected-to-normal vision (visual acuity ≤ 0.0 logMAR in each eye), (iv) have an uncorrected myopia < 0.50 D, hyperopia < 1.00 D, and astigmatism or anisometropia < 1.00 D, (iv) be free of any accommodative and binocular dysfunction following the recommendations of Scheiman & Wick (2008)[19], (v) scoring < 3 in the Stanford Sleepiness Scale (SSS),[27] and (vi) be soft contact lens users with at least one year of experience (when necessary). All participants had no history of adverse symptoms associated with caffeine intake and were neither pregnant nor breast-feeding, and they were instructed to avoid caffeine ingestion in the 24-hours prior to research participation. The experimental protocol followed the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB approval: 438/CEIH/2017).

Accommodation measurement

The Grand Seiko WAM-5500 open-field autorefractor (Grand Seiko Co. Ltd., Hiroshima, Japan) in Hi-Speed mode was used to measure accommodation. This apparatus has been clinically validated and permits a dynamic recording of refraction at a rate of ~ 5 Hz, with a sensitivity of 0.01 D.[28,29] Participants were asked to rest their forehead and chin in the corresponding supports while looking at Hart Charts through the open-field beam-splitter at distance (5 m) and near (40 cm). Subjects viewed both targets binocularly, but accommodation measures were only obtained from the sighting dominant eye, as determined by the hole-in-card method.[30] During dynamic recording, the examiner ensured that the instrument remained carefully aligned. Room illumination conditions were maintained at ~150 lux (Illuminance meter T-10, Konica Minolta, Inc., Tokyo, Japan) for both experimental sessions.

To measure the binocular accommodative facility, we followed a recently validated protocol from Vera et al. 2020[31], which is depicted in **Figure 1**. Participants were instructed to alternatively focus for 60 seconds on the distance Hart Charts mounted at eye level and on the near Hart Charts placed slightly inferior. The targets had a letter size of 11.2 mm and 0.9 mm (0.19 log MAR visual acuity for both charts), respectively, and the font type used was Helvetica (capital letters). The near target was held by a custom-made target which allowed to look at the far target without obstructing the participant´s view and with minimal vertical movement of the

eyes. Participants were asked to make sure that letters appear sharp before shifting their gaze to the other distance, and they did not have to name the letters during the test. The accommodative response measurement with the autorefractor was synchronized with the commencement of the test as the autorefractor produced a "beep" that indicated the start. Before the facility measurement, the accommodative response at 5 m and 40 cm was continuously monitored with the autorefractor over 60 secs to obtain the reference values used to analyze the accommodation accuracy of the binocular facility test (under-accommodated and under-relaxed) in each accommodation level and to evaluate the frequency of accommodative changes over the one-minute task. The far measurement was evaluated before the near measurement to avoid the possible effect of tonic accommodation.

To analyze the binocular accommodative facility, we estimated an approximate frequency by counting the zero-crossings of the accommodation measurement signal. We then estimated a sinusoid best fit for the signal at that frequency. Amplitude and phase were the free parameters for the Levenberg-Marquardt damped least-squares method. In addition, we removed all blinks and data recording errors by discarding data points ± 3 standard deviations away from the mean spherical refraction value. [28,32] To calculate the accommodative response at far and near distances, we subtracted the mean value from the dynamic measures and the baseline static refractive value to the accommodative demand for each distance (0.2 D and 2.5 D).[33] Finally, the accommodation measurement signal and the fitted sinusoid were compared and validated by cross-correlating the cleaned-up signal with the fitted sinusoid. We considered a normalized cross-correlation score > 0.8 to be a good fit. We implemented Matlab code to count the number of cycles, the percentage of incorrect cycles of accommodation and dis-accommodation (incorrect cycles divided by the total number of cycles), and the mean magnitude of accommodative change between the far and near.

[Figure 1 near here]

Procedure

Participants visited the laboratory on two separate occasions on different days (see **Figure 1** for a graphical overview of the experimental design). Both experimental sessions were scheduled at the same time of the day (± 1 hour) to avoid circadian variations. Participants were asked to refrain from alcohol and caffeine-based drinks 24 and 12h respectively before each experimental session and to sleep at least 7 h the night before testing. At the beginning of the first session, each participant underwent an optometric examination to verify that the inclusion criteria were fulfilled. From this moment on, both experimental sessions were identical except for the administration of a placebo or caffeine (~ 4 mg/kg) capsule. A pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) prepared both products and they were packaged in opaque gelatine capsules to avoid the identification of contents by colour, taste, or shape. Each placebo capsule contained 300 mg of corn-starch and the caffeine capsules (caffeine anhydrous) were dispensed in steps of 20 mg, being chosen based on the participant´s weight (~ 4 mg/kg).[34]

At the beginning of each experimental session, participants completed a self-rating scale (SSS) to check that the levels of alertness/sleepiness were similar between sessions.[35] The SSS contains seven statements ranging from 1 "Feeling active, vital, alert, or wide awake" to 7 "No longer fighting sleep, sleep onset soon, having dream-like thoughts". Participants were instructed to indicate which statement best described their actual state. Then, the capsule (placebo or caffeine) was prepared and coded by a third person. Participants rested for 60 minutes after capsule ingestion to reach a considerable plasma concentration,[36] and completed a visual analogous scale for assessing the activation level after capsule intake, this scale ranges from 1 "absolutely not activated" to 10 "extremely activated". After it, the accommodative response at far and near and the binocular facility test were recorded.

Statistical analysis

Before any statistical analysis, the normal distribution of the data (Shapiro-Wilk test) and the homogeneity of variances (Levene's test) were confirmed ($p > 0.05$). A t-test for related samples

was performed for the SSS survey to verify that participants attended with a similar level of alertness to both experimental conditions. A t-test for related samples with caffeine consumption (placebo, caffeine) as the only within-participants factor was carried out for the main experimental variables of accommodation facility (number of cycles, under-accommodated, under-relaxed, and accommodative magnitude), as well as for the perceived level of activation reported by participants. The magnitude of the differences was reported by Cohen's d. Statistical analyses were performed using the JASP statistics package (version 0.13.1.0).

Results

The analysis of subjective levels of sleepiness/alertness (SSS) reported by participants at the beginning of each experimental session corroborated that participants attended to the laboratory under similar levels of sleepiness/alertness ($p = 0.481$, Cohen´s $d = 0.16$). The perceived levels of activation after 60 minutes of caffeine ingestion showed a trend towards higher activation after caffeine intake in comparison to placebo ($p = 0.059$, Cohen´s $d = 0.45$; placebo = 6.8 ± 1.5 and caffeine 7.6 ± 1.8).

Data from the binocular accommodative facility test are displayed in **Table 1**. This set of results exhibited a statistically significant difference for the number of cycles ($p = 0.023$, Cohen's $d = 0.55$), showing a higher number of cycles in the caffeine when compared to the placebo condition. However, there were no statistically significant changes for the qualitative measures of the binocular accommodative facility (all p-values > 0.05).

[Table 1 near here]

Discussion

The present placebo-controlled, double-blind, balanced crossover study was designed to determine the impact of acute caffeine intake on the binocular accommodative facility. Our data revealed that caffeine intake increases the speed with which accommodation can be engaged and disengaged (i.e., a higher number of cycles), however, we did not observe any effect for the mean magnitude of accommodative change between the far and near targets, and the percentage of

correct cycles of accommodation and dis-accommodation. The current findings show that a single administration of caffeine (~ 4 mg/kg) enhances quantitative, but not qualitative, measures of accommodative facility.

The analyses of perceived levels of SSS before each experimental session confirmed that participants attended both experimental sessions with comparable levels of alertness/sleepiness. In addition, previous studies have demonstrated that caffeine ingestion produces stimulant-like subjective effects.[37] Although, the comparison of the level of activation after 60 minutes from caffeine and placebo consumption did not reach statistical significance ($p = 0.059$), the mean difference between both conditions (+0.8 in the caffeine condition) was similar to previous studies using the same amount of caffeine (difference ranging between 0.8 and 1.2).[26,38] Therefore, the caffeine-induced changes in the perceived levels of activation found in this study seem to agree with the previous evidence.

Caffeine acts as a stimulant of the central nervous system by blocking the adenosine receptors and stimulating a reflex activation of the sympathetic system.[39] Indeed, it has been demonstrated that several ocular indices that are regulated by autonomic innervation such as macular perfusion,[40] tear secretion,[41] intraocular pressure,[26] eye movements,[7] pupil size[11], and accommodative response[13] are modulated as a function of caffeine intake. Concerning the accommodative function, there is scientific evidence that caffeine modulates ocular accommodation functioning, increasing the accommodative amplitude[10] and improving the accommodative stability.[11,13] However, the magnitude of the accommodative response is unresponsive to caffeine intake.[11,13] Notably, the accommodative function is characterized by three measures, namely accommodative amplitude, response, and facility,[42] and to our knowledge, the only accommodative measure that has not been investigated after caffeine intake is the accommodative facility. The current findings are partially in line with studies that have reported a positive effect of caffeine on accommodation since we observed that caffeine ingestion improves the binocular accommodation facility by increasing the speed of accommodation and dis-accommodation from far (5 m) to near (40cm), and vice versa. However, we did not observe

any change in the magnitude of accommodative change between the far and near targets and the percentage of correct cycles. This finding agrees with the results of Redondo et al (2019),[11] as they did not observe changes in the static accommodative magnitude while looking at 5m and 40 cm between the caffeine and placebo conditions. Therefore, our results suggest that caffeine ingestion increases the speed of change in accommodation but not the quality variables of the accommodative change exerted to focus on both distances.

Accommodative facility depends on several visual and psychomotor factors such as ocular depth-of-focus, the velocity to stimulate or relax accommodation, the amplitude of the accommodative response, together with the subject's reaction time and visual processing.[22] It is well known that caffeine ingestion has positive effects on several psychomotor tasks and enhance fundamental aspects of cognitive performance, such as attention, vigilance, and reaction time,[43] which has been attributed to an increased global processing skill.[44] In addition, caffeine boosts visual processing, as it stimulates high-order visual attention, increases the selectivity of relevant information, and induces a faster identification of the stimulus.[5,45] All these attributes of caffeine may play a role in the higher number of accommodative cycles found in this study, which partially confirms our hypothesis. Therefore, it may be plausible that the irrelevant information was overlooked in the caffeine condition and led to faster identification of the accommodative stimuli. However, our experimental design cannot determine which is the main cause of the higher speed of change in accommodation because both the visual system and processing skills have been shown to be enhanced under the effects of caffeine. Future studies are required concerning this.

The ability to accurately accommodate and dis-accommodate has important implications in many daily activities (e.g., sports practice, driving, educational activities, etc.) that require fast shifts of visual attention to dynamic targets located at different distances. This study demonstrated that the accommodative facility can be enhanced by ingesting caffeine, which could improve performance in dynamic tasks. Nevertheless, further studies are required to test this hypothesis in applied scenarios. The current findings incorporate novel insights into the impact of caffeine intake on the dynamics of the accommodative function, however, this study presents some

limitations that should be acknowledged. First, the dose, the time elapsed after caffeine consumption, and habitual caffeine intake have been shown to influence the behavioral and physiological response to caffeine. Indeed, a recent study by Vera and colleagues (2019)[26] found that the ingestion of a caffeine pill (~ 4 mg/kg) caused a significant intraocular pressure rise, which was dependent on habitual caffeine intake and the time elapsed from caffeine intake. Here, we selected a dose of 4 mg/kg, a time lapse of 60 seconds, which is within the range of peak plasma (between 15 and 120 min),[46] and a group of low caffeine consumers, therefore, our results should be interpreted considering this. Future studies should consider determining the mediating role of these effects on the accommodative facility responsiveness to caffeine intake. Second, the method used for the qualitative and quantitative assessment of binocular accommodative facility was a validated tool that includes a specific letter size and levels of accommodation. It may be of interest to examine if any variations of the test (e.g., stimulus size, contrast, distance, etc.) could alter the effects of caffeine on the accommodative facility. Third, in ecological settings, the accommodative facility is performed in conjunction with different cognitive and physical demands (i.e., driving, sports, etc.). We recommend future studies to assess whether caffeine ingestion improves task performance in activities that require a correct integration of visual, physical, and/or cognitive skills.

Conclusions

The results of this placebo-controlled, double-blind, balanced crossover study showed that the ingestion of caffeine (~ 4 mg/kg) improved binocular accommodative facility, increasing the velocity to accommodate and relax accommodation. However, no caffeine-induced effects were observed for the mean magnitude of accommodative change between the far and near targets, as well as the percentage of correct cycles of accommodation and dis-accommodation. Our data suggest that the positive effects of caffeine on the binocular accommodative facility could improve performance in tasks that require shifting visual attention to stimuli located at different distances.

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Figure captions

Figure 1. A graphical illustration of the experimental design and the procedure followed to assess the binocular accommodative facility.

Table 1. Descriptive (mean ± standard deviation) and statistical values for the parameters obtained with the binocular accommodative facility test in the caffeine and placebo conditions.

	Caffeine	***Placebo***	***t***	***P-value***	***Cohen´s d (95% CI)***
Number of cycles (cpm)	30.85 ± 8.55	25.45 ± 9.47	2.48	0.023	0.55 (0.08 to 1.02)
Under-accommodated (%)	25.22 ± 33.18	32.80 ± 29.51	-1.13	0.271	-0.25 (-0.70 to 0.20)
Under-relaxed (%)	36.01 ± 41.80	24.61 ± 37.62	0.87	0.396	0.19 (-0.25 to 0.63)
Magnitude (D)	1.36 ± 0.41	1.33 ± 0.27	0.27	0.794	0.06 (-0.38 to 0.50)

Abbreviations: cpm = cycles per minute; D = diopters, CI = confidence interval